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Associations Between Depression, Arterial Stiffness, and Metabolic Syndrome Among Adults in the UK Biobank Population Study

A Mediation Analysis

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Key Points

Question

To what extent is the association of depression with peripherally assessed arterial stiffness mediated by metabolic syndrome?

Findings

In this large population-based cohort study of 124 445 adults aged 40 to 69 years, up to one-third of the association of depression with arterial stiffness was mediated by metabolic syndrome. The addition of inflammation to metabolic syndrome further increased the proportion of the mediated association of depression with arterials stiffness.

Meaning

Combined data on metabolic syndrome and inflammation may improve the early identification of future cardiovascular risk among adult patients with depression.

Abstract

Importance

Previous research has linked a history of depression with arterial stiffness (AS) during midlife.

Objective

To assess the association of depression with elevated midlife AS and to investigate the extent to which this association is mediated via metabolic syndrome (MetS).

Design, Settings, and Participants

This population-based retrospective cohort study analyzed data collected between March 2006 and December 2010 from 124 445 participants aged 40 to 69 years from the UK Biobank. Participants without data on AS at baseline (n = 332 780) or who reported a previous diagnosis of cardiovascular disease (n = 45 374) were not eligible. Data analysis was performed from May to August 2019.

Exposures

Lifetime history of depression was assessed via verbal interview and linked hospital-based clinical depression diagnosis. Metabolic syndrome was defined as the presence of 3 or more of hypertension, dyslipidemia, hyperglycemia, hypertriglyceridemia, and unhealthy waist circumference.

Main Outcomes and Measures

Peripherally assessed AS index (ASI) using digital photoplethysmography.

Results

Of 124 445 included participants with ASI assessed, 71 799 (57.7%) were women, and the mean (SD) age was 56 (8) years. A total of 10 304 participants (8.3%) reported a history of depression. Study findings indicated a significant direct association between depression and ASI levels (β = 0.25; 95% CI, 0.17-0.32). A significant indirect association was also observed between depression and ASI levels (β = 0.10; 95% CI, 0.07-0.13), indicating that 29% of the association of depression with ASI was mediated by MetS. The proportion of mediation increased to 37% when C-reactive protein was added to the MetS criteria (direct association: β = 0.21; 95% CI, 0.15-0.28; indirect association: β = 0.13; 95% CI, 0.10-0.17). Concerning components of MetS, the strongest indirect association was for waist circumference, accounting for 25% of the association between depression and ASI levels (direct association: β = 0.26; 95% CI, 0.18-0.34; indirect association: β = 0.09; 95% CI, 0.06-0.11). Among men, hypertriglyceridemia accounted for 19% of the association between depression and ASI (direct association: β = 0.22; 95% CI, 0.05-0.40; indirect association: β = 0.05; 95% CI, 0.02-0.08).

Conclusions and Relevance

One-third of the association of depression with elevated ASI levels during midlife may be accounted for by combined MetS and inflammatory processes. Unhealthy waist circumference and hypertriglyceridemia emerged as the most important potential targets for preventive interventions within women and men, respectively.

Introduction

People diagnosed with depression are at increased risk of major cardiovascular events (MACEs), including coronary heart disease and stroke.[1,2,3,4] Arterial stiffness (AS), a hardening of the artery wall because of aging and diverse pathologic states, is a key mediator of MACE,[5] and growing evidence has found an association of depression with AS.[6] Components of metabolic syndrome (MetS), such as hypertension, dyslipidemia, obesity, and hyperglycemia, represent leading promoters of AS.[5] Consistent with the key role of AS in predicting MACE incidence, carotid pulse wave velocity represents the criterion-standard measure for central AS,[7,8] and several other noninvasive techniques (eg, photoplethysmography) are available as indicators of specific AS parameters (eg, wave reflections).[5,9] While the interchangeability of these measures needs further research,[10] they were found to be independently associated with incident

MACE across different subgroups.[9,11,12] Therefore, a key unanswered question for public health is the extent to which the adverse effect of depression on MACE might be mitigated by targeting modifiable metabolic mediators. To address this concern, we need to better understand the role of MetS in mediating the association of depression with AS. The extent to which this mediation differs by sex is critical given that the prevalence of MACE, MetS, and depression is often greater among women compared with men.[13,14] Sex-specific mediating effects of MetS are generally underresearched but are a growing issue given the increasing prevalence of MetS in women.[15] The present study adopted a mediation analysis approach to quantify to what extent MetS and its individual components mediated the association of depression with AS. The study also aimed to investigate the extent to which the hypothesized mediation varied by sex.

Methods

Data

A population-based, retrospective cohort study was implemented within the 502 299 adults aged 40 to 70 years in the UK Biobank. These participants were recruited from 23 centers between March 2006 and December 2010 throughout the United Kingdom. Participants in the UK Biobank tended to be healthier than the general population, more likely to be women, and less likely to live in socioeconomically deprived areas relative to nonparticipants.[16] The study collected detailed phenotype and genotype data, including sociodemographic, lifestyle, clinical diagnosis, treatment, genetic, imaging, and physiological parameters. A detailed description of the UK Biobank data was provided elsewhere.[17] The North West Multi-centre Ethics Committee granted ethical approval to UK Biobank, and all participants provided written informed consent.

This study was restricted to a subset of participants with AS data available at the initial assessment (March 2006 to December 2010). Participants diagnosed with MACE (eg, angina, myocardial infarction, stroke, peripheral artery disease) or type 2 diabetes prior to AS assessment and those with treated hypertension or dyslipidemia prior to depression were excluded. Participants with a depression history prior to AS assessment represented the exposed group (n = 10 304), and those without a history of depression made up the comparison group (n = 114 141). A detailed description of the selection process for the study analytic sample is included in the (eFigure in the Supplement).

Outcome

The primary outcome measure was the AS index (ASI) derived from the analysis of digital volume pulse, an indirect method to assess AS peripherally.[18] Arterial stiffness index data were collected at baseline via the PulseTrace PCA 2 (careFusion), which uses finger photoplethysmography to assess the pulse waveform using an infrared sensor placed on the index finger of the participant's dominant hand.[19] The pulse waveform comprises a systolic peak and second diastolic peak, and the transit time (peak-to-peak time [PPT]) between the 2 peaks is related to the time it takes for the pulse wave to travel through the peripheral arterial tree.[20,21] This path length is proportional to a person's height (h), enabling the calculation of an index of large artery stiffness using the formula ASI = h / PPT.[21] The ASI was predictive of future risk of MACE[22] and was correlated with the pulse wave velocity.[20,23]

Exposure

The study used multiple sources to determine depression caseness. Self-reported data relied on the question, "In the touch screen you selected that you have been told by a doctor that you have other (non-cancer) serious illnesses or disabilities, could you now tell me what they are?" asked by a trained nurse during the verbal interview stage of data collection (at the time of AS assessment). The nurse used a tree

structure organized by system and loosely based on *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*), codes to record a depression diagnosis (UK Biobank field: 20002) using given codes (UK Biobank codes: 1286 and 1531). Linked hospital admission records were also used to identify a primary or secondary diagnosis of depression (*ICD-10* codes: F32 [single episode depression], F33 [recurrent depression], F34 [persistent mood disorders], F38 [other mood disorders], and F39 [unspecified mood disorders]). At baseline, participants also completed the 4-item Patient Health Questionnaire (PHQ-4), a brief screening tool that consists of a 2-item depression scale (PHQ-2) and the 2-item Generalized Anxiety Disorder scale.[24,25] Thus, caseness for depression was determined by a positive answer to the self-reported question, a primary or secondary diagnosis of clinic depression prior to AS assessment, or a score of 3 or more (cutoff score for depressive disorder[26]) on th PHQ-2 tool at the baseline assessment visit. Self-reported data on the year of the first depression diagno and the start date of a depression episode recorded in the hospital records were used to define a depress event prior to ASI assessment.

Mediators

The study's main mediator variable was MetS defined as the presence of 3 or more of the following: unhealthy waist circumference, hypertension, dyslipidemia, hypertriglyceridemia, and hyperglycemia.[27,28] These measures were assessed at the initial visit during which AS was measured. Waist circumference and blood pressure data were assessed by a trained nurse. Waist circumference was measured at the smallest part of the trunk using a 200-cm tape measure (SECA). We used established reference values for women (≥88 cm) and men (≥102 cm) as cutoff points for defining unhealthy waist circumference.[27] Two systolic and diastolic blood pressure measurements were taken after participants were at rest for 5 or more minutes using IntelliSense blood pressure monitor model HEM-907XL (Omron).[29] The mean of the 2 measures was used, and hypertension was defined as a systolic blood pressure of 130 mm Hg or greater or a diastolic blood pressure of 85 mm Hg or greater or as taking antihypertensive drugs. Dyslipidemia was defined as a high-density lipoprotein cholesterol level less than 40 mg/dL (to convert to millimoles per liter, multiply by 0.0259) among men and less than 50 mg/dL among women or as taking statin drugs. Hypertriglyceridemia was defined as triglyceride levels of 150 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0113) or taking triglyceride-lowering drugs. Hyperglycemia was defined as fasting blood glucose levels greater than 110 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or taking medication for diabetes. To evaluate recent evidence that C-reactive protein (CRP) adds prognostic value to subsequent risk of MACE,[30] a second MetS mediator was developed that also included high-sensitivity CRP as part of MetS. In line with previous research,[30,31] a cutoff point greater than 3.0 mg/L (to convert to nanomoles per liter, multiply by 9.524) for CRP concentration level was used as an indicator of elevated MACE risk. To ensure comparability, the same definition of MetS was used (ie, 3 or more metrics met). A self-reported antidepressant therapy variable was also developed to evaluate a potential mediating role for antidepressant medication.[32] Self-reported generic and trade names of current medications were recorded by a trained nurse. The British National Formulary was used as a guide to identify antidepressant drugs prescribed within the United Kingdom.

Covariates

Factors known to be associated with depression, ASI, and MetS were included in the analyses as confounders. These variables included self-reported age (linear and quadratic terms), sex (female vs male), race/ethnicity (recoded as white, black, Asian, mixed, and other), living in a socioeconomically deprived area (quintiles based on Townsend deprivation indices, an official measure for small-area [approximately 1500 residents] relative material deprivation), and parental history of severe depression as a marker of biological vulnerability.[33] Self-reported and Hospital Episode Statistics clinical data were used to identify predepression diagnoses of hypertension and high cholesterol as well as common long-term disorders

associated with depression and AS, including cancer, chronic kidney disease, inflammatory disorders (eg, rheumatoid arthritis, psoriasis), liver disease, and chronic obstructive pulmonary disease.[18,34,35] Self-reported data on the age at which current smokers started to smoke or the age ex-smokers stopped smoking were used to group participants into current smokers or nonsmokers prior to first depression episode.

Statistical Analysis

Descriptive statistics (eg, frequency, percentages, means, SDs) were used to contrast baseline differences among participants with depression and their comparison group without depression. To explicate the association of depression with AS, indirect associations acting through MetS as a mediating variable and direct associations not mediated by MetS and their SEs were quantified (Figure 1). A parametric regression approach (*paramed* package in Stata version 15 [StataCorp]) was used to estimate the total effect, the natural indirect effects (NIE), and natural direct effects (NDE) of depression on ASI.[36,37] Two models were estimated: a multivariate logistic regression model for MetS (mediator) conditional on depression (exposure) and all study confounders and a multivariate linear regression model for the ASI (outcome) conditional on depression, MetS, and all study confounders. The NDE represented the effect of depression on ASI that was independent of MetS. An NIE represented the proportion of depression that could be explained by its association with changes in MetS over time. The *paramed* approach was selected because it tested for the interaction between depression and MetS (or its individual subcomponents) in the ASI regression model using counterfactual definitions of direct and indirect effects.[36] To quantify the magnitude of mediation, the study estimated the proportion of the association mediated by MetS (NIE/[NDE + NIE]). Tests for interaction (*testparm* package) between sex and depression and between sex and MetS were statistically significant, and both pooled and sex-stratified mediation were estimated. All analyses were estimated using bootstrapping (500 replications) to recover the correct SEs for direct and indirect effects. Missing data on study variables ranged from 0% to 15% (eg, dyslipidemia), and multiple imputation using chained equations with 10 imputations was performed to optimize the validity of the findings. All *P* values were 2-tailed, and statistical significance was set at a *P* value less than .05.

To quantify the independent contribution of the individual components of MetS, the study also estimated mediation by these components in separate analyses. Planned additional sensitivity analyses were performed to examine the robustness of study results. First, the analyses were repeated using a lower threshold (2 or more factors) for MetS as well as defining MetS as a continuous variable to account for misclassification bias. Second, to account for protopathic bias, the analyses excluded all participants diagnosed with depression in the 12 months prior to the AS assessment. Third, we assessed a potential mediating role of current use of antidepressant medication. Since previous studies found no association of the type of antidepressant drugs with AS,[38] all antidepressant drugs were grouped together. To validate this procedure, additional analyses were performed using selective serotonin reuptake inhibitors and tricyclic drugs as independent mediators. Fourth, we estimated whether the mediation of MetS varied according to depression severity as assessed by the PHQ-4. Fifth, for comparative purposes, we excluded people with treated individual components of MetS.

Results

Of 124 445 included participants with ASI assessed, 71 799 (57.7%) were women, and the mean (SD) age was 56 (8) years. A total of 10 304 participants (8.3%) reported a history of depression, and 114 141 participants (91.7%) were without depression (eFigure in the Supplement). The median (interquartile range) time period from depression diagnosis to AS measurement was 12 (5-24) years. Table 1 shows sex-specific baseline characteristics for the depression and comparator groups. Relative to their comparison group, a higher proportion of men diagnosed with depression (30.4% [1051 of 3453] vs 20.1% [9910 of 49 193]) and women diagnosed with depression (26.2% [1796 of 6851] vs 19.3% [12 537 of 64 948]) lived in the most socioeconomically deprived areas by quintile. A total of 3681 women (53.7%) and 1715 men

(49.7%) with depression reported current use of antidepressant drugs compared with 2114 women (3.3%) and 705 men (1.4%) without depression. Metabolic syndrome was twice as common among women with depression (31.9% [2188 of 6851] vs 16.9% [10 976 of 64 948]) and men with depression (41.9% [1447 of 3453] vs 21.7% [10 666 of 49 193]) compared with those without depression. Figure 2 indicates that women and men with a history of depression presented with higher median values for ASI compared with the comparison group.

Table 2 presents the total, direct associations, and indirect associations of depression with ASI assessed peripherally. The indirect associations via MetS implied that we would, on average, observe a 0.10-point (95% CI, 0.07-0.13; $P = .001$) increase in ASI levels among participants with a history of depression. Th proportion of the association between depression and ASI mediated by MetS was 29%. The direct association of depression indicated that we would, on average, observe a 0.25-point (95% CI, 0.17-0.32 $< .001$) increase in ASI levels if all study participants were free of MetS. Similar trends emerged within sex-stratified analyses. Notably, the inclusion of CRP as an extra component of MetS increased the magnitude of MetS-mediated association to 37%, more so for men (to 52%) compared with women (to 34%).

Next, the study calculated the estimates of direct and indirect associations for specific subcomponents of MetS. As documented in Table 3, the MetS subcomponent that accounted for the largest proportion of the mediated association of depression with ASI was unhealthy waist circumference (25%), followed by CRP level (15%). Among men, hypertriglyceridemia was the subcomponent that accounted for the largest proportion (19%) of the indirect association between MetS and ASI ($\beta = 0.05$; 95% CI, 0.02-0.08; $P = .002$).

Additional Analyses

Analyses presented in eTable 1 in the Supplement revealed only a modest mediation of antidepressant medication use on the association of depression with peripheral ASI. Estimation models that adjusted for protopathic bias and those that excluded people with treated MetS components (eTable 4 in the Supplement) validated the study findings. A lower cutoff point (2 or more factors) for the MetS criteria resulted in an increase in the proportion of the association between depression and ASI mediated by MetS (44% vs 26%). Defining MetS as a continuous indicator modestly increased the estimates. No variation in estimates emerged according to the severity of depression or type of antidepressant drugs (eTable 2 in the Supplement).

Discussion

In a large population of middle-aged adults, a history of depression was associated with an increase in the risk of AS assessed peripherally, and this association was partly mediated through MetS. Specifically, 29% of the association of depression with ASI appeared to be mediated through MetS. The addition of high-sensitivity CRP to the MetS definition increased the proportion of the association between depression and ASI mediated by MetS, particularly among men (from 26% to 52%). Regarding individual components of MetS, unhealthy waist circumference mediated the highest proportion of the association of depression with ASI among women, while hypertriglyceridemia mediated the largest proportion of the association of depression with ASI within men.

Our study contributes to ongoing research efforts to better understand the risk of MACE associated with depression. Specifically, we identified combined MetS and inflammatory processes as a potentially influential indirect pathway from depression to ASI in a middle-aged adult population. This finding reinforces the value of developing effective complex interventions that target both MetS and inflammatory processes as means to prevent MACE among people diagnosed with depression. Abdominal obesity has been proposed to be the most prevalent form of MetS[39] and its magnitude to be directly related to MetS

prognosis.[40] These suggestions may account for waist circumference emerging as the strongest independent mediator in this study. Triglycerides are considered a clinical marker of excess abdominal obesity,[39] which may partly explain our study evidence around hypertriglyceridemia. Several explanations are possible for the unexplained proportion of depression associated with AS. For instance, psychological stress may cause deregulation in the sympathetic nervous system and hypothalamic-pituitary-adrenal axis,[41] which in turn can lead to AS[42] and elevated risk of MACE.[43] Relatedly, epigenetic factors linking depression and MACE through pathways not captured by this study could mediate AS. Early-life traumatic events (underlying depression) have lasting epigenetic effects via DNA methylation,[44] a process associated with incident MACE.[45] Our understanding of the genetic basis of depression is incomplete, a some of the unexplained risk of AS may also be due to unidentified genetic causes. The study attempted account for possible biological influences by adjusting for parental depression.

To our knowledge, this is the first study to document that the association between depression and increa AS[46,47,48] may be partly mediated via MetS. This estimation strategy may account for some of the inconsistent evidence about the association of depression with ASI in previous research.[49] As well as methodological concerns (eg, small samples, diverse depression criteria), prior studies have focused solely on the main effect of depression on AS and have overlooked the possibility of multiple pathways and processes (eg, MetS, inflammation) linking them. The difference in the strengths of the association of depression with AS across studies[47,49,50,51] implies the existence of several mechanisms mediating this association, as reported here. Further, our findings reinforce earlier evidence from different populations about the added prognostic information provided by CRP when incorporated into the MetS measure.[30] Our finding that the association of depression with ASI did not appear to be mediated by antidepressant medication use is in line with studies that found no link between antidepressant medication and ASI.[51,52] All MetS components (including CRP) are well-established risk factors for AS,[13,53] and our findings endorse these as important mediators for the association of depression with AS. A 2010 systematic review[54] identified obesity and hypertriglyceridemia as the strongest MetS individual predictors of atherosclerosis, which is in line with our findings.

Strengths and Limitations

In addition to the large population, the rich phenotypic data available within the UK Biobank allowed for data integration from multiple sources to define depression caseness. Additionally, the availability of objective measures of MetS and AS enhanced the robustness of our study findings.

Several limitations need consideration. A critical assumption of mediation analysis models is that of no exposure-induced mediator-outcome confounding, and any violation of this assumption would have implications for the identification of natural associations. If unmeasured confounders (eg, biological predisposition) are associated with the measured confounders (eg, parental depression) in a study, any potential influence of the former is at least partly removed via adjustment for the latter.[55] Another limitation is the self-reported data on depression that may have led to misclassification of depression caseness, which may not be random, although the inclusion of multiple data sources was adopted to attenuate misclassification bias. The study sample comprised middle-aged participants, which may limit the generalizability of the study findings to other population subgroups, especially in light of likely higher comedication rates in the US population.[56] The measurement of waist circumference in our study was found to result in lower mean values than more common measures based on umbilicus, iliac crest, or midpoint.[57] It is possible that defining hypertension, dyslipidemia, hypertriglyceridemia, and hyperglycemia to include those taking pharmacotherapy for these conditions may explain in part why waist circumference and triglycerides (less frequently treated pharmacologically compared with hypertension and hyperglycemia) prevailed as the most important contributors to the association of depression with AS. However, sensitivity analyses that excluded participants with treated MetS components validated the study

main findings. The UK Biobank used photoplethysmography as a measure of AS because of its ease of use and to mitigate operator-dependent variability. Photoplethysmography has been only moderately correlated with carotid pulse wave velocity,[20] as it relates best to peripheral AS rather than central AS, possibly reflecting different pathophysiological states. There is support for photoplethysmography repeatability,[20,58] and MetS was associated with increased photoplethysmography-assessed ASI.[59] Our research documented the prognostic value of ASI across multiple long-term disorders.[18] The study found no variation in MetS-mediated associations according to depression severity or type of antidepressant drug. Since only current use of antidepressant drugs was reported, we cannot exclude the possibility of an antidepressant treatment time lag associated with AS. However, the study findings are in line with evidence suggesting no variation in AS according to the type of antidepressant drug.[60]

Conclusions

While the systematic assessment of ASI in the general population is not currently recommended, it represents a promising screening tool to discriminate among subgroups at mild to moderate risk of future MACE.[61] Our study findings identified that about one-third of the proportion of the association between depression and ASI, and consequently, the risk of MACE, may be potentially prevented by addressing the combined effects of MetS and inflammation. This suggestion is contingent on the effective implementation of complex interventions (with several interacting components) targeting multiple MetS and inflammatory processes at the population level. The study also endorsed sex-specific preventive priorities for subcomponents of MetS, including waist circumference (in women) and hypertriglyceridemia (in men).

Notes

Supplement.

eTable 1. Adjusted natural direct and indirect associations of depression with arterial stiffness via antidepressant drugs.

eTable 2. Sensitivity analyses for adjusted natural direct and indirect associations of depression with arterial stiffness via metabolic syndrome.

eTable 3. Adjusted natural direct and indirect associations of depression severity with arterial stiffness via metabolic syndrome.

eTable 4. Adjusted natural direct and indirect associations of depression with arterial stiffness via subcomponents of metabolic syndrome after excluded treated events.

eFigure. Flow chart of the study sample.

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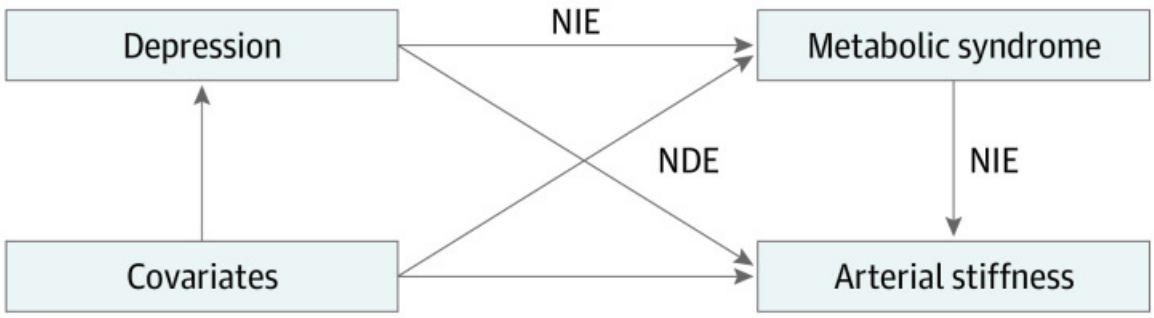
Figures and Tables

Figure 1.



Mediating Pathway of the Association of Depression With Arterial Stiffness

Direct acyclic graph of a structural model of mediation of the association between depression and arterial stiffness by metabolic syndrome. NDE indicates natural direct effects; NIE, natural indirect effects.

Table 1.

Participant Characteristics at the UK Biobank Assessment

Characteristic	No. (%)			
	Women		Men	
	With Depression (n = 6851)	Without Depression (n = 64 948)	With Depression (n = 3453)	Without Depression (n = 49 193)
Age, mean (SD), y	56 (8)	56 (8)	57 (8)	56 (8)
Living in the most socioeconomically deprived area by quintile	1796 (26.2)	12 537 (19.3)	1051 (30.4)	9910 (20.1)
Race/ethnicity				
White	6461 (94.3)	59 587 (91.7)	3244 (93.9)	45 200 (91.9)
Black	142 (2.1)	1958 (3.0)	101 (2.9)	1767 (3.6)
Asian	98 (1.4)	1618 (2.5)	37 (1.1)	1175 (2.4)
Mixed	70 (1.0)	592 (0.9)	32 (0.9)	334 (0.7)
Other	80 (1.2)	1193 (1.8)	39 (1.1)	717 (1.5)
Parental depression	2130 (31.1)	9275 (14.3)	947 (27.4)	5261 (10.7)
Hypertension	26 (0.4)	244 (0.4)	19 (0.6)	217 (0.4)
Hypercholesterolemia	7 (0.1)	96 (0.1)	4 (0.1)	75 (0.2)
Current smoker	1860 (27.1)	15 991 (24.6)	1279 (37.0)	15 998 (32.5)
Kidney disease	2 (0.03)	19 (0.03)	1 (0.03)	11 (0.02)
Cancer	76 (1.1)	185 (0.3)	15 (0.4)	53 (0.1)
Liver disease	7 (0.1)	23 (0.04)	11 (0.3)	34 (0.1)
COPD	4 (0.1)	46 (0.1)	4 (0.1)	31 (0.1)
Autoimmune disorder	47 (0.7)	233 (0.4)	20 (0.6)	89 (0.2)
Taking antidepressant drugs	3681 (53.7)	2118 (3.3)	1715 (49.7)	705 (1.4)
Metabolic syndrome	2188 (31.9)	10 976 (16.9)	1447 (41.9)	10 666 (21.7)
Hypertension	3890 (56.8)	35 986 (55.4)	2404 (69.6)	34 882 (70.9)
Dyslipidemia	2148 (31.4)	10 146 (15.6)	1381 (40.0)	7675 (15.6)
Hypertriglyceridemia	2497 (36.4)	16 659 (25.6)	1973 (57.1)	22 711 (46.2)
Hyperglycemia	1017 (14.8)	6371 (9.8)	642 (18.6)	5202 (10.6)

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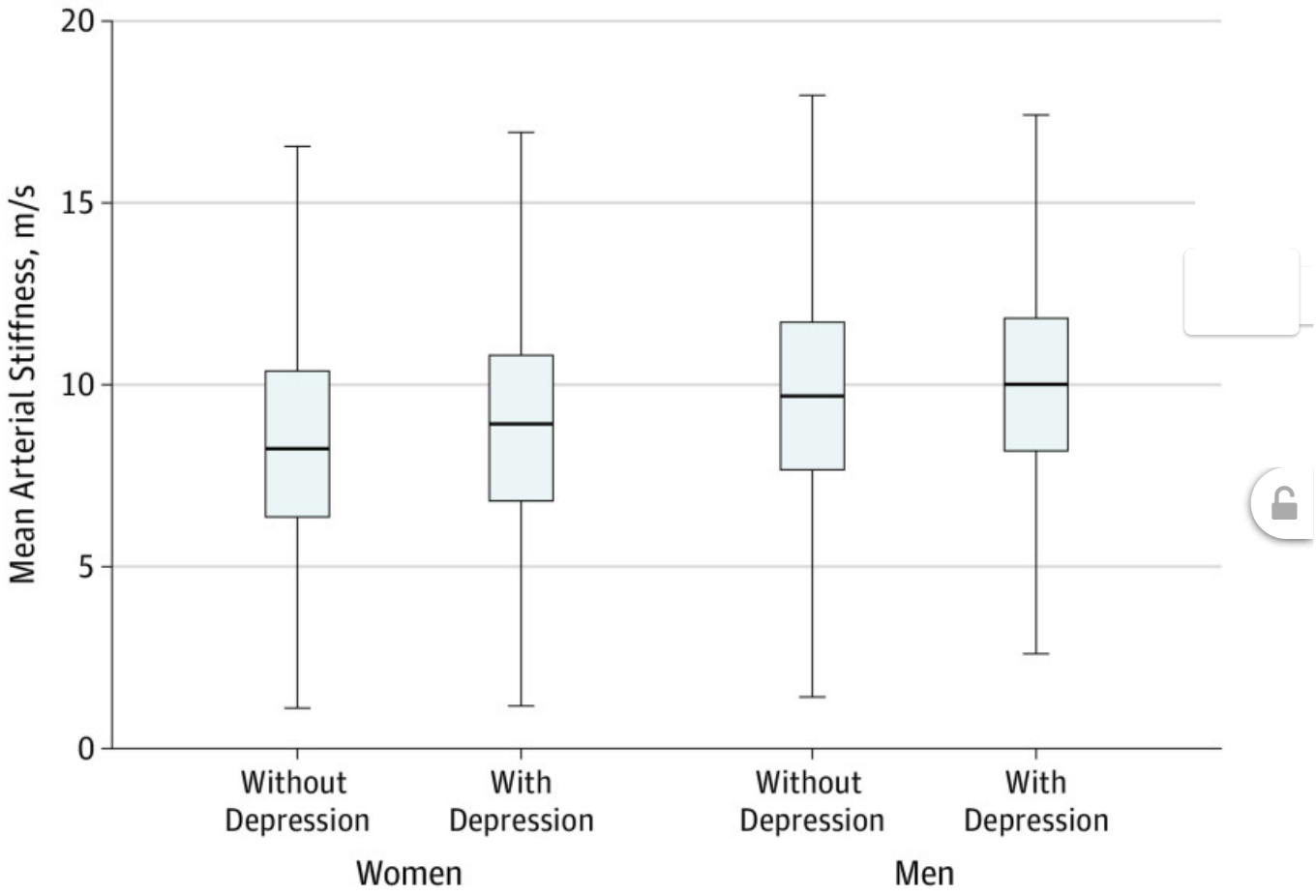
Abbreviation: COPD, chronic obstructive pulmonary disorder.

[a]Unhealthy waist circumference was defined as a cutoff point of 88 cm or greater for women and 102 cm or greater for men.

[b]High C-reactive protein was defined as a cutoff point greater than 3.0 mg/L (to convert to nanomoles per liter, multiply by 9.524).

Figure 2.



Mean Arterial Stiffness Index

Sex-specific mean arterial stiffness index values. Boxes contain 50% of the data, and the error bars contain the remainder. The horizontal lines indicate medians.

Table 2.

Adjusted Direct and Indirect Associations of Depression With Arterial Stiffness Mediated via Metabolic Syndrome (MetS)[a]

Measure	Overall (N = 124 445)		Women (n = 71 799)		Men (n = 52 646)	
	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
MetS						
Total association	0.35 (0.28-0.43)	<.001	0.38 (0.30-0.47)	<.001	0.27 (0.11-0.46)	<.001
Direct association	0.25 (0.17-0.32)	<.001	0.27 (0.19-0.34)	<.001	0.20 (0.03-0.42)	<.001
Indirect association via MetS	0.10 (0.07-0.13)	.001	0.11 (0.08-0.15)	.001	0.07 (0.01-0.14)	.004
Proportion mediated, %	29	NA	29	NA	26	NA
MetS and high-sensitivity CRP						
Total association	0.35 (0.28-0.43)	<.001	0.38 (0.30-0.47)	<.001	0.27 (0.11-0.45)	<.001
Direct association	0.21 (0.15-0.28)	<.001	0.25 (0.18-0.33)	.002	0.13 (−0.03 to 0.26)	.070
Indirect association	0.13 (0.10-0.17)	<.001	0.13 (0.10-0.16)	.051	0.14 (0.09-0.22)	<.001
Proportion mediated, %	37	NA	34	NA	52	NA

Abbreviations: CRP, C-reactive protein, NA, not applicable.

[a]Adjusted for age, sex, living in the most socioeconomically deprived areas by quintile, race/ethnicity, parental depression, hypertension, dyslipidemia, smoking, cancer, kidney disease, liver disease, chronic obstructive pulmonary disorders, and autoimmune disorders.

Table 3.

Adjusted Direct and Indirect Associations of Depression With Arterial Stiffness Mediated via Subcomponents of Metabolic Syndrome[a]

Association	Overall (N = 124 445)		Women (n = 71 799)		Men (n = 52 646)	
	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Hypertension						
Total association	0.34 (0.27 to 0.43)	<.001	0.38 (0.30 to 0.47)	<.001	0.27 (0.11 to 0.46)	.003
Direct association	0.33 (0.26 to 0.41)	<.001	0.36 (0.27 to 0.44)	<.001	0.27 (0.10 to 0.45)	<.001
Indirect association	0.01 (0.01 to 0.02)	.001	0.02 (0.01 to 0.03)	.001	0 (0 to 0.01)	.58
Proportion mediated, %	3	NA	5	NA	1	NA
Unhealthy waist circumference						
Total association	0.35 (0.28 to 0.43)	<.001	0.38 (0.05 to 0.35)	<.001	0.27 (0.11 to 0.46)	<.001
Direct association	0.26 (0.18 to 0.34)	<.001	0.28 (0.19 to 0.36)	<.001	0.22 (0.06 to 0.43)	<.001
Indirect association	0.09 (0.06 to 0.11)	<.001	0.11 (0.08 to 0.14)	<.001	0.05 (−0.01 to 0.10)	.05
Proportion mediated, %	25	NA	29	NA	19	NA
Dyslipidemia						
Total association	0.35 (0.28 to 0.43)	<.001	0.38 (0.30 to 0.47)	<.001	0.27 (0.10 to 0.46)	<.001
Direct association	0.30 (0.23 to 0.38)	<.001	0.32 (0.24 to 0.41)	<.001	0.24 (0.09 to 0.41)	<.001
Indirect association	0.05 (0.02 to 0.09)	<.001	0.06 (0.04 to 0.09)	<.001	0.02 (−0.05 to 0.12)	.44
Proportion mediated, %	14	NA	16	NA	7	NA
Hyperglycemia						
Total association	0.34 (0.27 to 0.43)	<.001	0.38 (0.30 to 0.47)	<.001	0.34 (0.21 to 0.51)	<.001
Direct association	0.33 (0.26 to	<.001	0.36 (0.28 to	<.001	0.34 (0.21 to	<.001

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Abbreviation: NA, not applicable.

[a]Adjusted for age, sex, living in the most socioeconomically deprived areas by quintile, race/ethnicity, parental depression, hypertension, dyslipidemia, smoking, cancer, kidney disease, liver disease, chronic obstructive pulmonary disorders, and autoimmune disorders.